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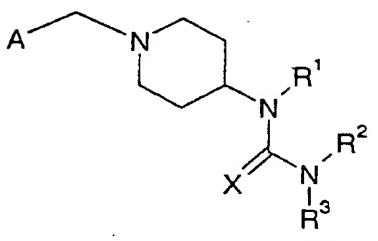
(54) Title: AMINOPIPERIDINE DERIVATIVES



(I)

(57) Abstract: The invention is concerned with novel aminopiperidine derivatives, a process for their manufacture, pharmaceutical compositions and the use of such compounds in medicine. In particular, the compounds of Formula (I) prevent the human immunodeficiency virus (HIV) from entering cells by blocking interaction of the viral envelope protein gp120 with a chemokine receptor on the cell surface. Consequently the compounds of this invention may be advantageously used as therapeutic agents for the treatment of diseases mediated by the human immunodeficiency virus (HIV), either alone or in combination with other inhibitors of HIV viral replication or with pharmacoenhancers. Disclosed are compounds of general formula (I) wherein R^1, R^2, R^3, X and A are as defined in the description.

Aminopiperidine Derivatives

The invention is concerned with novel aminopiperidine derivatives, a process for their manufacture, pharmaceutical compositions and the use of such compounds in medicine. In particular, the compounds prevent the human immunodeficiency virus (HIV) from entering cells by blocking interaction of the viral envelope protein gp120 with a chemokine receptor on the cell surface. Consequently the compounds of this invention may be advantageously used as therapeutic agents for the treatment of diseases mediated by the human immunodeficiency virus (HIV), either alone or in combination with other inhibitors of HIV replication or with pharmacoenhancers such as cytochrome P450 inhibitors.

HIV is the causative agent of acquired immunodeficiency syndrome (AIDS), a disease characterised by the destruction of the immune system, particularly of the $CD4^+$ T-cell, with attendant susceptibility to opportunistic infections. HIV infection is also associated with a precursor AIDS-related complex (ARC), a syndrome characterised by symptoms such as persistent generalised lymphadenopathy, fever and weight loss.

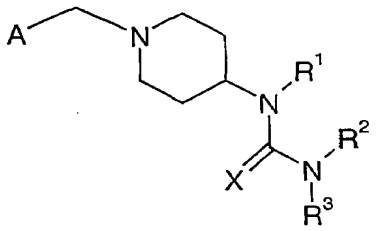
It has been reported [Liu et al., Cell 86, 367-377 (1996); Samson et al., Nature 382, 722-725 (1996); Dean et al., Science 273, 1856-1862 (1996)] that individuals who are homozygous for a deletion mutation in the CCR5 gene are highly resistant to infection by HIV, and that individuals heterozygous for this mutation have slowed disease progression [Huang et al., Nature Medicine 2, 1240-1243 (1996); Dean et al., Science 273, 1856-1862 (1996)]. Infection by HIV begins with attachment of the virus to a target cell, a process that requires the interaction of gp120 with both CD4 and a chemokine receptor (also termed a coreceptor) on the cell surface. Two important coreceptors for HIV infection are CXCR4 [Feng et al., Science 272, 872-877 (1996); Berson et al J Virol 70, 6288-6295 (1996)] and CCR5 [Alkhatib et al., Science 272, 1955-1958 (1996); Dragic et al., Nature 381, 667-673 (1996); Deng et al., Nature 381, 661-666 (1996)]. It is believed that binding to CD4 causes a conformational change in gp120 which then allows binding to the chemokine receptor [Deng et al., Nature 381, 661-666 (1996)]. Although many chemokine

receptors can serve as coreceptors for HIV in vitro, it is believed that the major coreceptor involved in sexual, parenteral and vertical transmission of HIV is the CCR5 receptor [van't Wout et al., J. Clin. Invest. 94, 2060-2067 (1994); Cornelissen, et al J.Virol. 69, 1810-1818 (1995); Veenstra et al., Clin. Infect. Dis. 21, 556-560 (1995)]. Viruses that use CCR5 as coreceptor have been termed R5 viruses, and it is believed that these are the key pathogenic strains of HIV in the majority of patients. Thus, blocking the interaction of HIV with CCR5 should prevent HIV infection of healthy individuals and should slow or halt viral spread and disease progression in infected individuals.

Cyclic amine derivatives are described in WO 99/38514 modulators of chemokine receptor activity.

The object of the invention, therefore, is to provide novel compounds which inhibit entry of HIV into target cells by binding to the CCR5 receptor, optionally without blocking chemokine binding, thereby preventing the interaction of HIV gp120 and CD4 with this receptor, and, accordingly, show a potential to be efficacious in the prevention and treatment of HIV-related diseases.

This object is achieved with the novel compounds of general formula I



I

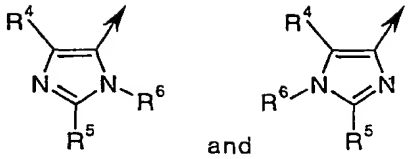
wherein

R^1 is hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl;

R^2 and R^3 are independently of each other hydrogen, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, allyl, substituted C_{1-4}-alkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl;

X is S or O;

A is selected from the group consisting of:



A1 and A2

wherein

R^4 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, CN, COR, CO_2R, CONRR', NHCOR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR';

R^5 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{1-4}-alkoxy, halogen, COR, aryl, substituted aryl, aryl-C(=O)-, substituted aryl-C(=O)-, aryl-CH(OH)-, substituted aryl-CH(OH)-, heterocyclyl, substituted heterocyclyl, heterocyclyl-C(=O)-, substituted heterocyclyl-C(=O)-, heterocyclyl-CH(OH)-, substituted heterocyclyl-CH(OH)- or NRR';

R^6 is hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{3-8}-cycloalkyl, COR, CO_2R, CONRR', NHCOR, SO_2NRR' or SO_2R;

R and R' are independently of each other hydrogen, C_{1-12}-alkyl, substituted C_{1-4}-alkyl, C_{3-8}-cycloalkyl, aryl, substituted aryl, heterocyclyl or substituted heterocyclyl;

as well as ethers or hydrolyzable esters of compounds of formula I and pharmaceutically acceptable salts thereof.

The term "alkyl" as used herein, and if not specified by the number of carbon atoms, denotes an optionally substituted straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl including their different isomers. The term "C_{1-12}-alkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms as defined above. The term

Chemokines and their receptors are potent activators and chemoattractants for leukocyte subpopulations and some non-hemopoietic cells. Whilst more studies are needed to delineate in more detail which chemokines and receptors are important in different diseases, they have been implicated in autoimmune disease [Arimilli et al Immunol. Rev. 177, 43-51 (2000)], diseases such as allergy, psoriasis, atherosclerosis, and malaria [Murdoch et al., Blood 95, 3032-3043 (2000)], multiple sclerosis [Zhang et al., Mult. Scler. 6, 3-13 (2000)], renal disease [Wada et al., Clin. Exp. Nephrol. 4, 273-280 (2000)], as well as in allograft rejection [Hancock et al., Curr. Opin. Immunol. 12, 511-516. (2000)].

CCR5, specifically, is believed to be the major coreceptor involved in sexual, parenteral and vertical transmission of HIV [van't Wout et al., J. Clin. Invest. 94, 2060-2067 (1994); Cornelissen, et al J.Virol. 69, 1810-1818 (1995); Veenstra et al., Clin. Infect. Dis. 21, 556-560 (1995)]. CCR5, specifically, may also have an etiological role in colitis [Ajuebor et al., J. Immunol. 166, 552-558 (2001)], multiple sclerosis [Simpson et al., J. Neuroimmunol. 108, 192-200 (2000)], diabetes [Cameron et al., J. Immunol. 165, 1102-1110 (2000)] and Alzheimer's disease [Xia and Hyman, Journal of Neurovirology 5, 32-41 (1999)].

The aminopiperidine derivatives provided by the present invention are useful in the treatment of the human or animal body. They can be used as medicaments, especially for treating viral diseases (HIV, HCV, and HBV infection), immune mediated conditions or diseases, bacterial diseases, parasitic diseases, inflammatory diseases, hyperproliferative vascular diseases, as anti-depressants, for the treatment of tumors, and cancer and to prevent allograft rejection. Especially, the present aminopiperidine derivatives are therapeutically active substances in the prevention and treatment of infection by the human immunodeficiency virus (HIV) and can be used as medicaments for the treatment of such diseases.

In particular, compounds of the present invention, and pharmaceutical compositions containing the same, are useful as chemotherapeutic agents, inhibitors of viral replication and modulators of the immune system. They can be used for the treatment of diseases mediated by retroviruses such as the human immunodeficiency virus (HIV), either alone or in combination with other inhibitors of HIV replication such as protease inhibitors, reverse transcriptase inhibitors and fusion inhibitors or with pharmacoenhancers such as cytochrome P450 inhibitors.

The aminopiperidine derivatives provided by the present invention can be used alone, or in combination with other therapeutically active agents, for example, an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-

parasitic agent, an anti-inflammatory agent, an anti-fungal agent and/or an anti-vascular hyperproliferation agent.

Compounds, whenever prepared by the processes of the present invention are also an object of the present invention.

Assay Method:

Resonance energy transfer assay (RET):

The activity of the compounds was determined using a fusion assay developed on the basis of the principle of resonance energy transfer, using HeLa cells stably transfected with gp120/gp41 from the macrophage-tropic primary isolate HIV-1JRFL and PM1 cells as previously described (Litwin, V et al (1996) "Human immunodeficiency virus type 1 membrane fusion mediated by a laboratory-adapted strain and a primary isolate analyzed by resonance energy transfer" J Virol 70(9), 6437-6441). The following minor modifications were applied: the assay buffer used comprised PBS/15%FCS (filtered through a 0.2uM filter); cells were not washed three times in PBS before reading; all compounds were tested in a final concentration of 1% DMSO, and the monoclonal antibody Leu3a (330ng/mL) was added to each plate, as a positive control (for 100% inhibition of cell fusion).

gp120-sCD4-CCR5 binding assay:

The gp120-sCD4-CCR5 binding assay was carried out as previously described (Dragic, T., A. Trkola, et al. (2000). "A binding pocket for a small molecule inhibitor of HIV-1 entry within the transmembrane helices of CCR5." Proc Natl Acad Sci U S A 97: 5639-44.) with the following minor modifications: the cell line used for these experiments was a CHO-K1 cell line stably transfected with the human CCR5 gene; the gp120-CD4 complex comprised recombinant biotinylated gp120 (JRFL strain) and soluble recombinant CD4; and all compounds were tested in a final concentration of 1% DMSO.

All reagents and cell lines were obtained from Progenics Pharmaceuticals Inc, Tarrytown, NY, USA, and are commercially available or can be prepared according to the methods described and the information given in the papers above.

In the assay, compounds of the formulas I range in activity from an IC_{50} of about 0.5 to about 1500 nM, with preferred compounds having a range of activity from about 0.5 to about 750 nM, more preferably about 0.5 to 300 nM, and most preferably about 0.5 to 50 nM.